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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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DETAILED ACTION

Status of Application

1. Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114.

2. Acknowledgement is made of applicant's filing of amendments/remarks on 12/19/2007. By the amendment, claims 37 and 72 have been amended; claims 49-52, 58-60, 71, 73 and 79 have been cancelled; and claim 80 has been newly added. Claims 37, 45-48, 53-54, 72, 75-78 and 80 are currently pending for prosecution on the merits.

3. Applicant's arguments with respect to claims 37, 45-54, 58-60, 71-73 and 75-79 have been considered but are moot in view of the new ground(s) of rejection.

4. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 37, 45-48, 53-54, 72, 75-78 and 80rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 37 and 72 recite "wherein the starting daily dosage is 250mg metformin and 1.25mg glyburide". The total amounts of drug combination provided as a starting

dose per day must be equal to 250 mg metformin and 1.25 mg glyburide. In other words, it cannot be go over the amount of 250 mg metformin and 1.25 mg glyburide during the first day of the treatment. However, the recitation of "wherein the metformin in said low dose combination is administered in a daily dosage in an amount within the range from about 160 mg to about 750mg..." in claim 37 and "the metformin in said low dose combination is administered in a daily dosage of at most about 750 mg" in claim 72 leave the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Similarly, the recitation of "the metformin in said low dose combination is administered in an amount within the range from about 160 to about 750 mg…." in claim 48, "the combination of metformin and glyburide in said low dose combination comprises a 250 mg metformin/1.25 mg....once a day or twice a day" in claim 53 and "the 250 mg metformin/1.25 mg glyburide dosage…twice daily…" in claim 54 renders the definition of the subject-matter of said claims unclear.

For the examination purpose, the term "the starting daily dosage is 250mg metformin and 1.25mg glyburide" is construed as "the treatment is initiated at 250 mg metformin and 1.25 glyburide dose".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 37, 45-48, 53-54, 72, 75-78 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barelli et al.(WO 97/17975, pub date: May 22, 1997, equivalent to US Patent 5,922,769) in view of Ohmura et al. (Current Therapeutic Research, Vol. 59, No. 12, December 1998, pp. 889-895), Drug Facts and Comparisons (1995 Edition, pp. 547) and Bauer et al. (US Patent 5,258,185, issue date: Nov. 2, 1993).

The claims are directed to a method of treating type 2 diabetes comprising administering to a drug naive human patient, as first line therapy, a low dose of a combination of metformin and glyburide where the daily dosage of metformin is 250mg; the daily dosage of glyburide is 1.25mg. Further limitations include: metformin and glyburide is formulated as a single dosage form (claim 45); weight ratio of metformin and glyburide is from about 400:1 to about 50:1 (claim 46); and that the glyburide having particular particle distributions and the patient population being drug naive patients as recited in the claims.

Barelli et al. teach a combination of metformin and glibenclamide (glibenclamide and glyburide are synonymous), in a weight ratio higher than 1:100, being useful for the treatment of type II diabetes (claims) and that the combination makes the therapeutical effect optimum at any

time of the progression of the disease, starting from the onset of the disease in NID diabetics (column 3, lines 19-20 and 49-50). Barelli et al. also disclose that the weight ratio of metformin and glibenclamide is 200:1 (column 2, lines 18-20) which overlaps with the claimed weight ratio; that said combination of dosages can be used starting from the onset of the disease in NID diabetics as long as the ratio of (higher than) 1:100 ratio between the two active principles is maintained, in both the multiple and submultiple dosages (column 3, lines 49-52 and 59-62); that "when the tablets are subdivided, thus obtaining minor and/or fractional daily dosages, the fixed ratio, which is the balanced..." (column 3, lines 52-55); that "the therapeutic rationale of said studies suggested the use of combined formulations of medicaments capable of finding a remedy for both the deficiency in insulin secretion and the insulin-resistance condition" (column 1, lines 48-55); and that "the combined therapy (sulfonylurea+biguanide) palys therefore a specifically important therapeutical role, since it allows to obtain an effective metabolic control in those patients with diabetes of type II, in which the therapy with only sulfonylureas or only biguanides becomes ineffective with time" (column 1, lines 62-67). Barelli et al. further teach a single coated tablet in EXAMPLE 1 (column 9, lines 25-26) which contains 500 mg metformin and 5 mg glibenclamide.

Ohmura et al. teaches the efficacy of low-dose metformin alone or combination of sulfonylurea (e.g., glibenclaimide) in the treatment of type 2 diabetes mellitus, wherein metformin is started at 250mg dose and titrated up to 750mg daily (pages 890-891 and 894).

Facts and Comparisons is being supplied as a supplemental reference to demonstrate the state of art knowledge in using 1.25 mg glyburide as a known antidiabetic agent (for patient who may be more sensitive to hypoglycemic drugs).

Bauer et al. teaches pharmaceutical formulations of glibenclamide rapidly releasing the active substance for the treatment of diabetes (see abstract). Bauer et al. disclose improved drug release and bioavailability (column 2, lines 17-22) of the drug glibenclamide by using a preparation having micronized glibenclamide with mean particle size of ±5 μm which overlaps with the instantly claimed particle size of 2- 60 μm.

The difference between Barelli et al.'s teaching and the instant claimed invention lies in that Barelli et al. do not explicitly teach (i) the patient population being drug naive patients or the first line treatment of diabetes, (ii) a low dose of a combination of 250mg and 1.25mg glyburide as starting dosage, (iii) so that daily dosage of metformin is 750mg or less, and (iv) glyburide having particular particle distributions.

With regard to the patient population, although Barelli et al. do not explicitly teach that the combination is administered to a drug naive patient as a first line therapy, Barelli et al. do disclose that the combination teaches a therapeutic effect for treating type 2 diabetes, optimum at any time of the progression of the disease, starting from the onset of the disease in NID diabetics. Since the patient population of Barelli et al.'s method of treatment is type 2 diabetic, without identifying a patient's drug status and treatment history, one having ordinary skill in the art still would have been motivated to treat a drug naïve patient with Barelli et al.'s combination of metformin and glyburide as a first line therapy. Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the treatment

of Barelli et al. in view of Bauer et al. to result in the practice of the instant invention with a reasonable expectation of success.

With respect to the recitation of metformin dosage being 250 mg and glyburide dosage being 1.25 mg, although Barelli et al. do not explicitly teach this particular dosage, Barelli et al. have provided guidance that 1500mg metformin and 15 mg glyburide are the maximum recommended daily dosage in the combination (column 3, lines 37-40) with recommended weight ratio of greater than 100:1, particularly 200:1 (column 2, line 20) between metformin and glyburide. Furthermore, Barelli et al. teaches that the tablets can be "subdivided, thus obtaining minor and/or fractional daily dosages, the fixed ratio, which is the balanced...". Thus, one having ordinary skill would have expected as taught by Ohmura et al. (Current Therapeutic Research, Vol. 59, No. 12, December 1998, pp. 889-895) and Drug Facts and Comparisons (1995 Edition, pp. 547) that initiating therapy with 250 mg metformin and 1.25 mg glyburide would be useful for the treatment of type 2 diabetes mellitus patient, especially for patients who are more sensitive to hypolgycemic drugs.

The determination of the appropriate dosage amounts of active ingredients for a treatment is routinely made by those of ordinary skill in the art and is well within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information of the active ingredient disclosed in the prior art. Thus, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to determine the amounts of metformin and glyburide for achieving the therapeutic effect of treating type 2

diabetes without significant adverse effects to result in the pharmaceutical composition as claimed with a reasonable expectation of success.

Applicant's attention is further drawn to MPEP at §2144.05, which states, "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage range is the optimum combination of percentages.., where the general condition of a claim are disclosed in the prior, it is not inventive to discover the optimum or workable ranges by routine experimentation."

With respect to the specific particle distribution of glyburide, Bauer et al. teaches pharmaceutical formulations of glibenclamide rapidly releasing the active substance for the treatment of diabetes (see abstract). Bauer et al. disclose improved drug release and bioavailability (column 2, lines 17-22) of the drug glibenclamide by using a preparation having micronized glibenclamide with mean particle size of $\pm$5 μm which overlaps with the instantly claimed particle size of 2- 60 μm. Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to prepare micronized glibenclamide for the combination of metformin and glibenclamide as disclosed by Barelli et al. in view of Bauer et al. to result in the drug combination of the instant invention, motivated by Bauer et al. that glibenclamide is virtually water-insoluble (column 2, line 9) and micronized glibenclamide improves its solubility and bioavailability (column 2, lines 31-32). Although the prior art does not discloses the instant "at most 25% of the particles are less than 11 μm and at most 25% are greater than 46 μm". However, one having ordinary skill in the art would have expected at the time of the invention was made that the specific particle distribution percentage of the instant

claims would have been characteristic of the modified prior art method. Generally, differences in a particle distribution percentage or concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such particle distribution concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it not inventive to discover the optimum or workable particle distribution percentage or concentration by routine experimentation.

With respect to the recitation of claim 54 regarding patient baseline measurements, those values are the same as those measured for the type 2 diabetic patient as disclosed by Barelli et al. (column 4, lines 23-29).

With respect to the recitation of "lowering blood glucose in a hyperglycemic human patient, decreasing insulin resistance, decreasing hemoglobinAlc, increasing post-prandial insulin levels or decreasing prandial glucose excursion" in claim 72, since the drug combination of metformin and glyburide is the same as what's disclosed in the prior art and are being administered to the same patient population, the recited effects are expected and thus do not limit the claims.

Although the instant claims use the different names for the said ingredients than those taught in the cited references, these references are particularly pertinent and relevant because all the claimed species and their roles are well taught in the cited reference. Thus, one would have

been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Conclusion

6.

7. No Claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system,

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